# Transformation of aldehydes into nitriles in an aqueous medium using *O*-phenylhydroxylamine as the nitrogen source

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# Transformation of aldehydes into nitriles in an aqueous medium using *O*-phenylhydroxylamine as the nitrogen source

The conversion of an aldehyde into a nitrile can be efficiently performed using *O*-phenylhydroxylamine hydrochloride in buffered aqueous solutions. The reported method is specifically optimized for aqueous-soluble substrates including carbohydrates. Several reducing sugars including monosaccharides, disaccharides, and silyl-protected saccharides were transformed into cyanohydrins in high yields. The reaction conditions are also suitable for the formation of nitriles from various types of hydrophobic aldehyde substrates. Furthermore, cyanide can be eliminated from cyanohydrins, analogous to the Wohl degradation, by utilizing a readily-removed weakly basic resin as a promoter.

Keywords: nitriles; cyanohydrin; saccharide; Wohl degradation

A nitrile is an important functional group in organic synthesis because it can be transformed into several functional groups such as an amine,[1,2] carboxylic acid,[3,4] ester,[5,6] ketone,[7] and heterocycles.[8,9] Furthermore, nitriles are utilized in many fields beyond organic chemistry including pharmaceutical[10] and materials.[11,12] In the past decades, several methods have been reported for the formation of nitriles from different functional groups such as amines, amides, and alcohols. However, these methods require harsh conditions or metal-complex catalysts.[13]

The usage of aldehydes as precursors to nitriles is common due to the mild reaction conditions and the readily available substrates. Formation of nitriles through dehydration of oximes is one of the most simple methods.[14] In general, an aldehyde is reacted with hydroxylamine to form an aldoxime followed by dehydration with acetic anhydride, thionyl chloride, or lead oxide to form the desired nitrile.[14,15] However, these dehydration conditions often require an excess of dehydrating agents or high temperatures resulting in low functional group tolerance.[16] To avoid using harsh

conditions and increase the compatibility of the reaction with a variety of functional groups, several approaches have been reported to convert aldehydes into nitriles in a one-pot manner using various nitrogen sources[16-18] such as *O*-(diphenyl-phosphinyl)hydroxylamine (**DPPH**),[19] hydroxylamine-*O*-sulfonic acid,[20] and *N*-hydroxyphthalimide.[21]

Although many publications reported the formation of nitriles from organic aldehydes, only a few examples studied cyanohydrin formations from reducing sugars.[22] Cyanohydrins are versatile structures as ligands in catalysis or as intermediates in the synthesis of biologically active compounds. [23-25] Herein, a method optimized for the formation and isolation of cyanohydrins from reducing sugars is described. *O*-Phenylhydroxylamine hydrochloride (**$H_2$NOPh**) was used as a nitrogen source, and the reaction proceeded under the aqueous condition at room temperature.

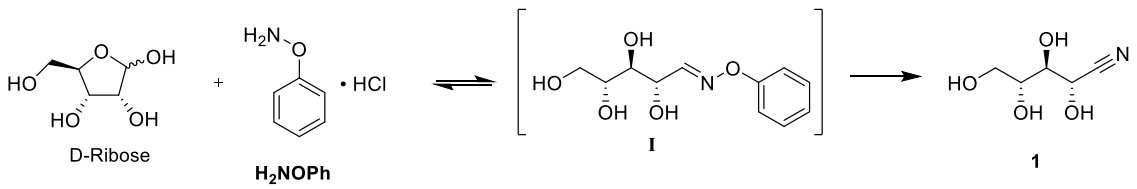
In a preliminary study, the reaction of D-ribose and **$H_2$NOPh** in an aqueous solution yielded cyanohydrin (**1**). This observation led to an evaluation of the reaction conditions under various aqueous environments at room temperature (Table 1). All aqueous solutions in the optimization studies were prepared from deuterium oxide, which allowed for monitoring the reaction by $^1$H NMR spectroscopy. The NMR spectra demonstrated that the oxime was formed as an intermediate (**I**), then phenol was subsequently eliminated,[26] and the cyanohydrin (**1**) was obtained as a product (Scheme 1). When the shelf-stable and commercially available *O*-phenylhydroxylamine is used as the hydrochloride salt, a significant decrease in pH is observed. At low pH (entries 1 and 2), the aldehyde substrate was not fully consumed in the 7 h timeframe of the reaction screen. However, the formation of cyanohydrin could proceed to the completion under phosphate buffered conditions at pD 5.45 and pD 7.25 within 7 h (entries 3 and 4). The pD values of the reaction mixtures in entries 3 and 4 were monitored, and the changes of

the pD values were not observed. It was reasoned that under the buffered conditions, the hydrochloric acid produced from the starting material was neutralized which allowed the oxime intermediate to be fully formed. Based on these investigations, the reaction condition of 0.2 M of sodium phosphate buffer at pD 7.25 was used as a general procedure for further studies.

**Table 1. Optimization study with D-ribose.**

| Entry | Condition | Yield[a] (%) |
|---|---|---|
| 1 | $D_2O$ | 83 |
| 2 | 1% Acetic acid in $D_2O$ | 83 |
| 3 | 0.2 M Sodium phosphate in $D_2O$ pD[b] 5.45 | 100 |
| 4 | 0.2 M Sodium phosphate in $D_2O$ pD[b] 7.25 | 100 |

[a]Determined by $^1$H NMR; [b]pD = pH + 0.45 (Ref. 31)

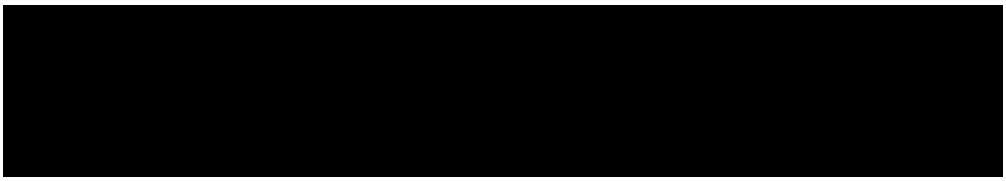



Scheme 1. Proposed reaction mechanism.

Next, various types of hydroxylamines were evaluated for the formation of a cyanohydrin from D-Ribose under the standard condition of 0.2 M sodium phosphate pD 7.25 (Table 2). The reactions were monitored by $^1$H NMR spectroscopy for 24 h at room temperature. As expected, the cyanohydrin product was not obtained from the reaction of

D-ribose with *O*-benzylhydroxylamine hydrochloride (entry 2); however, only an oxime was observed. The cyanohydrin was obtained from the reaction of D-ribose with hydroxylamine-*O*-sulfonic acid in 90% yield after 24 h (entry 3). For the reaction of D-ribose with **DPPH** and *O*-(mesitylsulfonyl)-hydroxylamine (entries 4 and 5, respectively), only a trace of cyanohydrin product was observed. The poor solubility of both substrates in water was believed to be a major reason. The quantitative yield from entry 1 demonstrated that **$H_2NOPh$** was a suitable nitrogen source for the formation of cyanohydrins from a variety of carbohydrates under an aqueous condition.

**Table 2. Evaluation of cyanohydrin formation with hydroxylamine sources.**



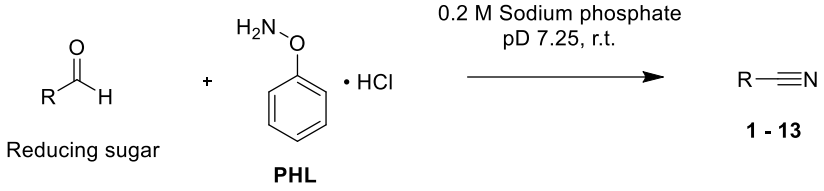
| Entry |  | Yield[a] (%) |
|---|---|---|
| 1 |  | 100 |
| 2 |  | 0 |
| 3 |  | 90 |
| 4 |  | trace |
| 5 |  | trace |

[a]Determined by $^1$H NMR.

The transformation of 13 reducing sugars to cyanohydrins is reported in Table 3. All carbohydrate substrates were reacted with **$H_2NOPh$** in 0.2 M sodium phosphate at pD 7.25 and the reactions were monitored by $^1$H NMR spectroscopy. Phenol produced as a byproduct could be easily removed from the reaction mixtures by extraction with diethyl

ether. In most cases, after evaporation of the aqueous solution to dryness, the cyanohydrin products were obtained by dissolving the dried mixture with ethanol. For hydrophobic substrates, such as silyl-protected carbohydrates (entry 13), the products were purified by silica gel chromatography. The reactions of **$H_2NOPh$** with pentoses (entries 1 to 4) proceeded within 12 h to obtain cyanohydrins in 81–100% yields. A longer reaction time was needed for the substrate 2-deoxy-D-ribose (entry 5) to obtain the cyanohydrin in 96% yield. The reactions of hexoses (entries 6 to 8) were slower and often required 48 h to provide the cyanohydrin products in 63–97% yield. However, the stereochemistry of C-2 dramatically affects the rate of the reaction. As shown in entry 9, the reaction of D-mannose required only 24 h for the full conversion (96% yield). Maltose is a highly polar disaccharide that is poorly soluble in ethanol. Although the $^1$H NMR of crude from the reaction of maltose after 48 h indicated that the reaction went to a completion, the isolated yield was lower than expected (53% yield, entry 10) because the product maltonitrile could not be fully extracted using ethanol from the solid crude. L-Fucose, GlcNAc, and silyl-protected ribose (entries 11, 12, and 13, respectively) were rather sluggish (72 h), but still produced nitriles in good yields (59–70% yield).

**Table 3. Transformation of reducing sugars to cyanohydrins.**




| Entry | Reducing sugar | Time (h) | R—≡N | Yield[a] (%) |
|---|---|---|---|---|
| 1 | D-Ribose | 12 | [redacted] 1 | 94 |
| 2 | D-Arabinose | 12 | [redacted] 2 | 83 |
| 3 | D-Xylose | 12 | [redacted] 3 | 98 |
| 4 | L-Arabinose | 12 | [redacted] 4 | 100 |
| 5 | 2-Deoxy-D-ribose | 16 | [redacted] 5 | 96 |
| 6 | D-Glucose | 48 | [redacted] 6 | 90 |
| 7 | D-Galactose | 48 | [redacted] 7 | 97 |
| 8 | D-Allose | 48 | [redacted] 8 | 63 |
| 9 | D-Mannose | 24 | [redacted] 9 | 96 |

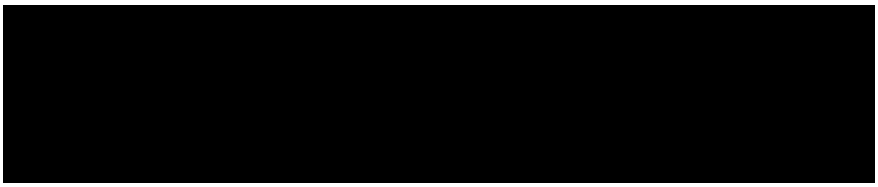
| | | | | |
|---|---|---|---|---|
| 10 | D-Maltose | 48 |  | 53 |
| 11 | L-Fucose | 72 |  | 59 |
| 12 | N-Acetyl-D-glucosamine (GlcNAc) | 72 |  | 70 |
| 13 | 5-*O*-TBDPS-D-ribose[b,c] | 72 |  | 69 |

[a]Isolated yield; [b]MeOH was added (50% v/v) to increase solubility; [c]TBDPS = tert-butyldiphenylsilyl.

The scope of the aldehyde substrates was extended to aromatic, aliphatic, and α,β-unsaturated aldehydes. However, the reaction conditions used for carbohydrate compounds needed to be modified for these hydrophobic substrates because they are poorly soluble in water. Furthermore, the deuterated conditions were replaced with the protonated solvents because the reactions could simply be monitored by TLC. A 4:1 ratio of methanol to 0.5 M of sodium phosphate pH 6.5 was found to be the best condition for dissolving most organic compounds. The reactions were conducted at 60 °C with varying reaction times depending on the type of aldehyde substrates resulting in acceptable to good isolated yields (Table 4). The transformation of aromatic aldehydes into nitriles appeared to be fast and provided exceptional yields. Entry 1 shows that 4-hydroxy-3-

methoxybenzonitrile was obtained in 99% yield after 8 h. The reaction of unsaturated aromatic and aliphatic aldehyde (entries 2 and 3) required a longer reaction time (24 – 48 h) to obtain the desired nitrile products in 63% and 58% yield, respectively. These reaction conditions were also compatible with an acid-labile functional group. Entry 4 shows that *N*-Boc-4-piperidine-acetaldehyde was transformed into the corresponding nitrile in 60% yield after 72 h.

**Table 4. Transformation of aldehydes to nitriles.**



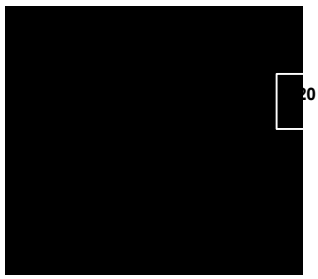
| Entry |  | Time (h) | Yield[a] (%) |  |
|---|---|---|---|---|
| 1 |  | 8 | 99 |  |
| 2 |  | 72 | 63 |  |
| 3 |  | 24 | 58 |  |
| 4 |  | 72 | 60 |  |

[a]Isolated yield

Wohl degradation was selected to demonstrate the utility of the cyanohydrins formed from reducing sugars. Wohl degradation is one of the most common methods of shortening aldose sugars through the formation of an acetylated cyanohydrin and the elimination of cyanide using ammonia or silver hydroxide.[27,28] To perform this cyanide elimination on the unprotected cyanohydrins formed above, it was necessary to find a base that can be easily removed from the reaction mixture due to the challenges of isolating unprotected carbohydrates.

Weakly basic resins (WBS) can be conveniently removed by filtration and are particularly well suited for the removal of ionic impurities from aqueous solutions.[29,30] To our best knowledge, WBS has never been used for shortening carbohydrates. It was hypothesized that the tertiary amine-functionalized resin would promote the nucleophilic elimination of cyanide from the cyanohydrin. Three cyanohydrins (compound **7**, **9** and **10**) were chosen to demonstrate a Wohl-type degradation using Lewatit MP 62 (tertiary amine) resin as a base. The mixture was stirred in ethanol at 70 °C for 7 h to obtain the desired products in moderate isolated yields. As shown in Table 5, D-Galactonitrile (**7**) was shortened to D-lyxose (**18**) in 79% yield (entry 1), and D-mannonitrile (**9**) was shortened to D-arabinose (**19**) in 75% yield (entry 2). The same reaction condition was applied to complex saccharides. Entry 3 shows that cyanide was eliminated from a D-maltonitrile (**10**) to form D-glucopyranose-(1→3)-D-arabinopyranose (**20**) in 60% yield. The Wohl-type degradation is one practical application of cyanohydrins produced from reducing sugars.

**Table 5. Degradation of cyanohydrins.**

| Entry |  | Product | Yield[a] (%) |
|---|---|---|---|
| 1 |  |  | 79 |
| 2 |  |  | 75 |
| 3 |  |  | 60 |

[a]Isolated yield

## Conclusion

A new method for transforming aldehydes into nitriles using commercially available *O*-phenylhydroxylamine hydrochloride as a nitrogen source is described. The method works exceptionally well under aqueous solution in the presence of sodium phosphate buffer. Several reducing sugars were transformed to cyanohydrins in high yields. Poor aqueous solubility of an aldehydes often results in longer reaction times and diminished yields. This method was modified to be compatible with hydrophobic compounds by using a mixture of an organic solvent and sodium phosphate buffer. Several functionalized aliphatic and aromatic aldehydes were transformed into nitriles in

acceptable yields. The reaction conditions were also suitable for compounds with a range of functional groups including acid-labile functionalities. Furthermore, a method for shortening reducing sugars by using weakly basic resins was demonstrated. The cyanohydrin compounds (**7**, **9** and **10**) were used as reactants for the demonstration. The reducing sugars obtained from the degradation of D-galactonitrile, D-mannonitrile, and D-maltonitrile were D-lyxose (**18**), D-arabinose (**19**), and D-glucose-α-(1→3)-D-arabinose (**20**), respectively.

## Experimental section

### *General procedures*

All chemicals and reagents were purchased and used without further purification. Deuterium oxide buffer solution was prepared by dissolving 0.227 g of $Na_2HPO_4$ and 0.221 g of $NaH_2PO_4$ in 16 mL of deuterium oxide and measured the pD value of the buffer solution by pH meter. It is worth noting here that the pH meter was calibrated with aqueous ($H_2O$) calibration buffer. Therefore, pD was calculated based on Krezel and Bal [31] (pD = pH + 0.45). Concentrated phosphoric acid and 1 M NaOH in deuterium oxide were used to adjust the pD values. Lewatit MP 62 resin was purchased from Sigma and washed with ethanol through the vacuum filtration before used. Optical rotation was measured on a Jasaco DIP-370 digital polarimeter. $^{1}H$ and $^{13}C$ NMR spectra were recorded on an Varian INOVA 400 FT-NMR (400 MHz, 101 MHz), Varian Unity 400 FT-NMR (400 MHz, 101 MHz), and Bruker AVANCE NEO 500 (500 MHz, 126 MHz) respectively. Chemical shifts are reported in ppm and multiplicities are reported as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), hep (heptet), m (multiplet), and br (broad). For $^{13}C$ NMR spectra of samples in the $D_2O$ solvent, a small

amount of methanol was added as the internal standard. Thin-layer chromatography (TLC) analysis was performed on silica gel 60 with fluorescent indicator $F_{254}$ (EMD Millipore) and visualized with UV light (254 nm) where applicable. Silica gel column chromatography was performed on SiliaFlash® F60 (Silicycle, 40-64 μm). Mass spectrometry analysis was performed by the School of Chemical Sciences Mass Spectrometry Laboratory at the University of Illinois.

***Disposal***

Cyanide is highly toxic and should be handled and disposed properly. Since cyanide can eliminate from cyanohydrins, all products and waste should be disposed in a separate waste container with clearly labelled. The cyanide gas produced from the elimination of cyanohydrin was stored as NaCN solution by trapping the gas with 5% NaOH solution.

***General procedure for the formation of cyanohydrins***

To a 7 mL vial was added reducing sugar (1 equiv), *O*-phenylhydroxylamine hydrochloride (**$H_2$NOPh**) (1.2 equiv), and 0.2 M sodium phosphate pD 7.25 to the final concentration of 0.1 M. The reaction was stirred at room temperature until the oxime intermediates were disappeared (monitored by $^1$H NMR). Then, the reaction mixture was transferred into a separatory funnel and washed with diethyl ether for 10 times. The remaining aqueous solution was evaporated to dryness. Ethanol was added to the solid residue to extract the product from the phosphate salt. The phosphate salt residues in the ethanol solution were removed by centrifugation. The solvent was evaporated to obtain the desired product.

***D-Ribonitrile*** **(1)**

Prepared according to the general procedure using D-ribose (0.0226 g, 0.150 mmol) as reducing sugar. Yield = 0.0208 g (94%). $[\alpha]_D^{20}$ + 8.1 (*c* 0.58, $H_2O$). $^1H$ NMR (400 MHz, $D_2O$) δ (ppm): 4.88 (d, *J* = 3.5 Hz, 1H, H-2), 3.88 – 3.75 (m, 2H, H-3 and H-4), 3.72 – 3.60 (m, 2H, H-5a and H-5b). $^{13}C$ NMR (101 MHz, $D_2O$) δ (ppm): 119.2, 72.5, 72.1, 63.6, 63.0. HR-MS (ESI) m/z calcd. for $C_5H_9NO_4Na$ $(M + Na)^+$ 170.0429, found 170.0431.

***D-Arabinonitrile*** **(2)**

Prepared according to the general procedure using D-arabinose (0.0086 g, 0.0577 mmol) as reducing sugar. Yield = 0.0071 g (83%). $[\alpha]_D^{20}$ - 20.8 (*c* 0.34, $H_2O$). $^1H$ NMR (400 MHz, $D_2O$) δ (ppm): 4.90 (d, *J* = 2.3 Hz, 1H, H-2), 3.85 – 3.76 (m, 2H, H-3 and H-5a), 3.76 – 3.70 (m, 1H, H-4), 3.66 (dd, *J* = 11.6, 5.4 Hz, 1H, H-5b). $^{13}C$ NMR (126 MHz, $D_2O$) δ (ppm): 120.4, 72.0, 70.5, 63.2, 62.3. HR-MS (ESI) m/z calcd. for $C_5H_9NO_4Na$ $(M + Na)^+$ 170.0429, found 170.0434.

***D-Xylonitrile*** **(3)**

Prepared according to the general procedure using D-xylose (0.0489 g, 0.326 mmol) as reducing sugar. Yield = 0.0471 g (98%). $[\alpha]_D^{20}$ + 7.5 (*c* 0.63, $H_2O$). $^1H$ NMR (400 MHz, $D_2O$) δ (ppm): 4.71 (dd, *J* = 5.8, 0.9 Hz, 1H, H-2), 3.91 – 3.80 (m, 2H, H-3 and H-4), 3.69 – 3.54 (m, 2H, H-5a and H-5b). $^{13}C$ NMR (101 MHz, $D_2O$) δ (ppm): 119.8, 72.0, 71.2, 62.9, 62.7. HR-MS (ESI) m/z calcd. for $C_5H_9NO_4Na$ $(M + Na)^+$ 170.0429, found 170.0434.

***L-Arabinonitrile*** **(4)**

Prepared according to the general procedure using L-arabinose (0.046 g, 0.307 mmol) as reducing sugar. Yield = 0.0455 g (100%). $[\alpha]_D^{20}$ + 18.4 (*c* 0.59, $H_2O$). $^1H$ NMR

(400 MHz, $D_2O$) δ (ppm): 4.89 (d, *J* = 2.2 Hz, 1H, H-2), 3.84 – 3.75 (m, 2H, H-3 and H-4), 3.74 – 3.68 (m, 1H, H-5a), 3.65 (dd, *J* = 11.6, 5.5 Hz, 1H, H-5b). $^{13}C$ NMR (101 MHz, $D_2O$) δ (ppm): 120.4, 72.1, 70.5, 63.2, 62.3. HR-MS (ESI) m/z calcd. for $C_5H_9NO_4Na$ $(M + Na)^+$ 170.0429, found 170.0433.

***2-Deoxy-D-ribonitrile* (5)**

Prepared according to the general procedure using 2-deoxy-D-ribose (0.0114 g, 0.085 mmol) as reducing sugar. Yield = 0.0107 g (96%). $[\alpha]_D^{20}$- 6.9 (*c* 0.27, $H_2O$). $^1H$ NMR (400 MHz, $D_2O$) δ (ppm): 3.99 – 3.91 (m, 1H, H-3), 3.84 – 3.71 (m, 1H, H-5a), 3.70 – 3.56 (m, 2H, H-4 and H-5b), 2.87 (ddd, *J* = 17.2, 4.1, 0.5 Hz, 1H, H-2a), 2.77 (ddd, *J* = 17.2, 6.8, 0.5 Hz, 1H, H-2b). $^{13}C$ NMR (101 MHz, $D_2O$) δ (ppm): 120.0, 74.0, 67.7, 62.9, 22.6. HR-MS (ESI) m/z calcd. for $C_5H_9NO_3Na$ $(M + Na)^+$ 154.0480, found 154.0484.

***D-Gluconitrile* (6)**

Prepared according to the general procedure using D-glucose (0.0082 g, 0.045 mmol) as reducing sugar. Yield = 0.0072 g (90%). $[\alpha]_D^{20}$ + 15.4 (*c* 0.38, $H_2O$). $^1H$ NMR (400 MHz, $D_2O$) δ (ppm): 4.72 (d, *J* = 7.3 Hz, 1H, H-2), 4.06 (dd, *J* = 7.4, 1.6 Hz, 1H, H-3), 3.82 (dd, *J* = 11.8, 2.4 Hz, 1H, H-6a), 3.79 – 3.70 (m, 2H, H-4 and H-5), 3.64 (dd, *J* = 11.5, 5.3 Hz, 1H, H-6b). $^{13}C$ NMR (101 MHz, $D_2O$) δ (ppm): 119.8, 71.2, 71.1, 70.1, 63.5, 63.2. HR-MS (ESI) m/z calcd. for $C_6H_{11}NO_5Na$ $(M + Na)^+$ 200.0535, found 200.0528.

***D-Galactonitrile* (7)**

Prepared according to the general procedure using D-galactose (0.0162 g, 0.090 mmol) as reducing sugar. Yield = 0.0155 g (97%). $[\alpha]_D^{20}$ + 11.3 (*c* 0.19, $H_2O$). $^1H$ NMR (400 MHz, $D_2O$) δ (ppm): 4.91 (d, *J* = 1.9 Hz, 1H, H-2), 3.96 – 3.86 (m, 2H, H-3 and H-6a), 3.68 – 3.62 (m, 3H, H-4, H-5, and H-6b). $^{13}C$ NMR (101 MHz, $D_2O$) δ (ppm): 120.6,

71.5, 70.4, 69.2, 63.6, 62.4. HR-MS (ESI) m/z calcd. for $C_6H_{11}NO_5Na$ $(M + Na)^+$ 200.0535, found 200.0540.

***D-Allonitrile* (8)**

Prepared according to the general procedure using D-allose (0.0139 g, 0.077 mmol) as reducing sugar. Yield = 0.0086 g (63%). $[\alpha]_D^{20}$ + 2.9 (*c* 0.20, $H_2O$). $^1H$ NMR (400 MHz, $D_2O$) δ (ppm): 4.87 (dd, *J* = 3.9, 1.1 Hz, 1H, H-2), 3.96 (ddd, *J* = 7.6, 3.9, 1.1 Hz, 1H, H-3), 3.91 – 3.84 (m, 1H, H-5), 3.78 – 3.70 (m, 2H, H-4, H-6a), 3.63 (ddd, *J* = 11.9, 7.3, 1.1 Hz, 1H, H-6b). $^{13}C$ NMR (101 MHz, $D_2O$) δ (ppm): 119.5, 73.0, 72.7, 72.4, 63.7, 62.7. HR-MS (ESI) m/z calcd. for $C_6H_{11}NO_5Na$ $(M + Na)^+$ 200.0535, found 200.0540.

***D-Mannonitrile* (9)**

Prepared according to the general procedure using D-mannose (0.0335 g, 0.186 mmol) as reducing sugar. Yield = 0.0317 g. (96%). $[\alpha]_D^{20}$ - 11.6 (c 0.57, $H_2O$). $^1H$ NMR (400 MHz, $D_2O$) δ (ppm): 4.62 (d, *J* = 8.4 Hz, 1H, H-2), 4.03 (dd, *J* = 8.3, 1.5 Hz, 1H, H-3), 3.81 (dd, *J* = 11.7, 2.6 Hz, 1H, H-6a), 3.75 – 3.69 (m, 1H, H-5), 3.68 – 3.58 (m, 2H, H-4 and H-6b). $^{13}C$ NMR (101 MHz, $D_2O$) δ (ppm): 120.9, 71.0, 70.8, 69.1, 63.7, 62.7. HR-MS (ESI) m/z calcd. for $C_6H_{11}NO_5Na$ $(M + Na)^+$ 200.0535, found 200.0537.

***D-Maltonitrile* (10)**

Prepared according to the general procedure using D-maltose (0.0355 g, 0.098 mmol) as reducing sugar. Yield = 0.0186 g. (53%). $[\alpha]_D^{20}$ + 80.3 (*c* 0.39, $H_2O$). $^1H$ NMR (400 MHz, $D_2O$) δ (ppm): 5.08 (d, *J* = 3.7 Hz, 1H, H-1B), 4.91 (d, *J* = 5.4 Hz, 1H, H-2A), 4.12 (ddd, *J* = 5.3, 3.9, 1.1 Hz, 1H, H-3A), 3.92 (m, 2H, H-4A and H-6A), 3.86 – 3.61 (m, 6H, H-5A, H-6A', H-3B, H-5B, H-6B and H-6B'), 3.55 (dd, *J* = 10.0, 3.9 Hz, 1H, H-2B), 3.40 (t, *J* = 9.6 Hz, 1H, H-4B). $^{13}C$ NMR (101 MHz, $D_2O$) δ (ppm): 119.8,

101.5, 101.3, 80.4, 73.3, 72.9, 72.7, 72.3, 70.0, 63.0, 62.9, 61.0. HR-MS (ESI) m/z calcd. for $C_{12}H_{21}NO_{10}Na$ $(M + Na)^+$ 362.1063, found 362.1060.

***L-Fuconitrile* (11)**

Prepared according to the general procedure using L-fucose (0.0133 g, 0.0812 mmol) as reducing sugar. $CD_3OD$ (20% v/v) was added to the reaction to increase the solubility. Yield = 0.0078 g (59%). $[\alpha]_D^{20}$ - 16.9 (*c* 0.19, $H_2O$). $^1H$ NMR (400 MHz, $D_2O$) δ (ppm): 4.92 (d, *J* = 2.0 Hz, 1H, H-2), 4.11 – 4.03 (m, 1H, H-5), 3.85 (dd, *J* = 9.5, 2.1 Hz, 1H, H-3), 3.46 (dd, *J* = 9.5, 1.6 Hz, 1H, H-4), 1.23 (d, *J* = 6.5 Hz, 3H, H-6). $^{13}C$ NMR (101 MHz, $D_2O$) δ (ppm): 120.6, 72.6, 71.9, 66.1, 62.6, 19.2. HR-MS (ESI) m/z calcd. for $C_6H_{11}NO_4Na$ $(M + Na)^+$ 184.0586, found 184.0591.

***N-Acetyl-D-glucosaminonitrile* (12)**

Prepared according to the general procedure using *N*-acetyl-D-glucosamine (0.0250 g, 0.114 mmol) as reducing sugar. Yield = 0.0174 g (70%). $[\alpha]_D^{20}$ + 36.8 (*c* 0.19, $H_2O$). $^1H$ NMR (400 MHz, $D_2O$) δ (ppm): 4.93 (d, *J* = 8.2 Hz, 1H, H-2), 4.25 (dd, *J* = 8.2, 0.7 Hz, 1H, H-3), 3.89 – 3.82 (m, 1H, H-5), 3.77 – 3.73 (m, 2H, H-4 and H-6a), 3.70 – 3.59 (m, 1H, H-6b), 2.06 (s, 3H, $COCH_3$). $^{13}C$ NMR (101 MHz, $D_2O$) δ (ppm): 174.9, 117.8, 71.2, 70.4, 69.4, 63.5, 57.2, 22.4. HR-MS (ESI) m/z calcd. for $C_8H_{14}N_2O_5Na$ $(M + Na)^+$ 241.0800, found 241.0803.

***Synthesis of 5-O-Tert-Butyl-Diphenylsilyl-D-Ribonitrile (13)***

To a 7 mL vial was added 5-*O*-tert-butyl-diphenylsilyl-D-ribose (0.131 g, 0.337 mmol, 1 equiv), *O*-phenylhydroxylamine hydrochloride (**$H_2NOPh$**) (0.059 g, 0.404 mmol, 1.2 equiv), 2 mL of 0.2 M sodium phosphate pD 7.25 and 2 mL of methanol. The reaction was stirred at room temperature until the change of starting materials could not be observed (monitored by TLC). The reaction mixture was evaporated to dryness. The crude mixture was purified by silica column ($R_f$ = 0.3, 40:60 EtOAc:Hexanes) with a

gradient of 20:80 to 40:60 (EtOAc:Hexanes). Yield = 0.0895 g (69%). $[\alpha]_D^{20}$ + 11.4 (*c* 0.08, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.76 – 7.56 (m, 4H, Ar-H), 7.55 – 7.34 (m, 6H, Ar-H), 4.77 (d, *J* = 3.9 Hz, 1H, H-2), 3.93 – 3.81 (m, 3H, H-3, H-4, and H-5a), 3.78 (dd, *J* = 8.0, 4.3 Hz, 1H, H-5b), 1.08 (s, 9H, -tBu). $^{13}$C NMR (101 MHz, $CDCl_3$) δ (ppm): 135.7, 132.5, 130.4, 128.2, 118.0, 72.8, 71.7, 64.6, 64.3, 27.0, 19.4. HR-MS (ESI) m/z calcd. for $C_{21}H_{28}NO_4Si$ $(M + H)^+$ 386.1788, found 386.1789.

***General Procedure for the Formation of nitriles***

To a 7 mL vial, aldehyde (1 equiv) and *O*-phenylhydroxylamine hydrochloride (**$H_2$NOPh**) (1.2 equiv) were dissolved in 4:1 of methanol:0.5 M sodium phosphate pH 6.5 to the final concentration of 0.1 M. The reaction was stirred at 60 °C until the changes of starting materials could not be observed (monitored by TLC). Then, the reaction mixture was cooled to room temperature and extracted with 3 mL $CH_2Cl_2$ a total of 5 times. The combined organic layer was dried over $Na_2SO_4$ and concentrated by rotary evaporator. The crude product was purified by silica column chromatography.

***4-Hydroxy-3-methoxybenzonitrile*** **(14)**

Prepared according to the general procedure using vanillin (0.0254 g, 0.167 mmol) as an aldehyde. The reaction time was 8 h. The crude product was purified by silica column chromatography (EtOAc:Hexanes 40:60). Yield = 0.0248 g (99%). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.22 (dd, *J* = 8.2, 1.8 Hz, 1H, Ar-H), 7.08 (d, *J* = 1.7 Hz, 1H, Ar-H), 6.96 (d, *J* = 8.2 Hz, 1H, Ar-H), 3.92 (s, 3H, -$OCH_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ (ppm): 150.0, 146.7, 127.1, 119.4, 115.3, 113.8, 103.4, 56.4. HR-MS (ESI) m/z calcd. for $C_8H_8NO_2$ $(M + H)^+$ 150.0555, found 150.0557

***Trans-Cinnamonitrile*** **(15)**

Prepared according to the general procedure using *trans*-cinnamaldehyde (0.025 g, 0.189 mmol) as an aldehyde. The reaction time was 72 h. The crude product was purified by silica column chromatography (EtOAc:Hexanes 10:90). Yield = 0.0155 g (63%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.49 – 7.36 (m, 6H, Ar-H and =CH), 5.88 (d, *J* = 16.7 Hz, 1H, =CH). $^{13}$C NMR (101 MHz, $CDCl_3$) δ (ppm): 150.7, 133.6, 131.4, 129.3, 127.5, 118.3, 96.4. HR-MS (ESI) m/z calcd. for $C_9H_7N$ $(M)^{+\cdot}$ 129.0578, found 129.0581.

***(3S)-Citronellylnitrile* (16)**

Prepared according to the general procedure using *(-)*-citronellal (0.0244 g, 0.158 mmol) as an aldehyde. The reaction time was 24 h. The crude product was purified by silica column chromatography (EtOAc:Hexanes 5:95). Yield = 0.0139 g (58%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.07 (tt, *J* = 7.1, 1.5 Hz, 1H, =CH), 2.42 – 2.16 (m, 2H, -$CH_2$), 2.10 – 1.95 (m, 2H, -$CH_2$), 1.86 (m, *J* = 13.1, 6.5 Hz, 1H, -CH), 1.68 (s, 3H, =$CCH_3$), 1.61 (s, 3H, =$CCH_3$), 1.46 – 1.22 (m, 2H, -$CH_2$), 1.07 (d, *J* = 6.7 Hz, 3H, -$CH_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ (ppm): 132.4, 123.6, 119.0, 36.0, 30.1, 25.8, 25.4, 24.6, 19.5, 19.5. HR-MS (ESI) m/z calcd. for $C_{10}H_{17}N$ $(M)^{+\cdot}$ 151.1361, found 151.1368. Optical rotation data reported previously.[32]

***N-Boc-4-(cyanomethyl)piperidine* (17)**

Prepared according to the general procedure using *N*-Boc-4-piperidine-acetaldehyde (0.0308 g, 0.136 mmol) as an aldehyde. The reaction time was 72 h. The crude product was purified by silica column chromatography (EtOAc:Hexanes 40:60). Yield = 0.0183 g (60%). $^{1}$H NMR (101 MHz, $CDCl_3$) δ (ppm): 4.14 (s, 2H, -$CH_2$), 2.70 (t, *J* = 12.2 Hz, 2H, -$CH_2$), 2.30 (d, *J* = 6.4 Hz, 2H, -$CH_2$), 1.93 – 1.73 (m, 3H, -$CH_2$ and -CH), 1.44 (s, 9H, -tBu), 1.32 – 1.17 (m, 2H, -$CH_2$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ

(ppm): 154.7, 118.2, 79.8, 43.5, 33.5, 31.4, 28.6, 24.2. HR-MS (ESI) m/z calcd. for $C_{12}H_{20}N_2O_2Na$ $(M + Na)^+$ 247.1422, found 247.1430

***General Procedure for the Elimination of Cyanohydrins***

To a 20 mL vial was added sugar cyanohydrin and ethanol to a final concentration of 0.01 M. Lewatit MP 62 resins (approximately 10 times by mass compared to the mass of cyanohydrin) were added to the mixture then the vial was connected to a gas bubbler with a 5% NaOH trap by way of a Tygon® tube and host adapter. The purpose of this apparatus was to trap cyanide gas produced during the reaction. The reaction was stirred (300 rpm) at 70 °C for 7 h. The resins were removed by vacuum filtration, and the solution was evaporated to obtain the desired product.

**Preparation of D-Lyxose (18)**

Prepared according to the general procedure using D-galactonitrile (0.0058 g, 0.033 mmol) as sugar cyanohydrin. Yield = 0.0039 g (79%).

**Preparation of D-Arabinose (19)**

Prepared according to the general procedure using D-mannonitrile (0.0065 g, 0.0365 mmol) as sugar cyanohydrin. Yield = 0.0041 g (75%).

**Preparation of α-D-Glucopyranosyl-(1→3)-D-Arabinopyranose (20)**

Prepared according to the general procedure using D-maltonitrile (0.0037 g, 0.01 mmol) as sugar cyanohydrin. Yield = 0.0018 g (58%). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.41 (d, $J$ = 3.8 Hz, 1H, Glc-H-1), 5.22 (d, $J$ = 3.3 Hz, 0.5H, Ara-H-1β), 4.65 (d, $J$ = 7.9 Hz, 0.5H, Ara-H-1α), 4.05 – 3.58 (m, 9H), 3.47 (t, $J$ = 9.5 Hz, 1.5H, Glc-H-4), 3.35 – 3.30 (m, 0.5H, Ara-H-2α). $^{13}$C NMR (126 MHz, $D_2O$) δ (ppm): 100.0, 96.2, 92.4, 77.3, 77.1, 76.7, 76.4, 75.1, 74.6, 74.5, 73.7, 73.3, 73.2, 72.2, 72.1, 70.4, 70.0, 69.8,

61.2, 61.0. HR-MS (ESI) m/z calcd. for $C_{11}H_{19}O_{10}$ $(M-H)^-$ 311.0978, found 311.0977.

Optical rotation data reported previously.[33]

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